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### REMARKS

#### **I. STATUS OF THE CLAIMS.**

Claims 321-350 are presently pending. Claims 321, 335, and 342 have been amended as discussed below. Support for these amendments is provided throughout the specification, including at, e.g., page 131, lines 12-32. All of the amendments herein are fully supported by the specification and none of the amendments constitutes new matter as discussed in further detail below.

#### **II. AMENDMENTS TO THE SPECIFICATION.**

The specification has been amended to correct several inadvertent typographical and grammatical errors. For example, the term "CD28BP-12" has been corrected to recite properly "CD28BP-15." The term "CTLA4" has been corrected to recite properly "CTLA-4". The term "FLAG-tag" in the paragraph beginning at page 219, line 1 has been amended to recite properly the term "FLAG<sup>TM</sup> tag", as suggested by the Examiner. In addition, the paragraph beginning at page 21, line 13 has been amended to recite properly "FLAG<sup>TM</sup> epitope". The paragraph beginning at page 131, line 12 has been amended to correct inadvertent typographical error, as shown by the corresponding paragraph on page 133, lines 16-17. The paragraphs beginning at page 5, line 29, page 43, line 14, and page 78, line 10 have been amended to correct an inadvertent grammatical errors. Several inadvertent spelling errors have also been corrected. No new matter is added by these amendments.

#### **III. REJECTION UNDER 35 USC § 101.**

Claims 321-341 and 348-350 were rejected under 35 USC §101 because the claimed invention is allegedly drawn to non-statutory subject matter. This rejection has been overcome by amending claims 321, 335, and 342 to specify an isolated or non-naturally occurring polypeptide as suggested by the Examiner. Applicants thank the Examiner for his helpful suggestions. Withdrawal of the rejection is respectfully requested.

#### **IV. REJECTION UNDER 35 USC § 112.**

Claims 321-350 were rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for a polypeptide variant of an extracellular domain of a wild-

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type primate B7-1 comprising a polypeptide sequence that differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by specifically defined amino acid substitutions, allegedly does not reasonably provide enablement for a genus of polypeptide variants of an extracellular domain of a wild-type primate B7-1 comprising a polypeptide sequence that differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by at least one amino acid, and which comprises the substitution of an amino acid other than alanine at an amino acid residue position corresponding to position 65 of wild-type human B7-1. Office Action, pp. 4-5. Specifically, the Examiner takes the position that "the claims as presently recited encompass in their breath any polypeptide which does not have an alanine or tyrosine at position 65. In the absence of a defined common structure that must be maintained by members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention." *Id.* at p. 5.

This rejection has been overcome by the amendments to independent claims 321, 335, and 342. As amended, claim 321 specifies more particularly an isolated or non-naturally occurring polypeptide variant of an extracellular domain of a wild-type primate B7-1 comprising a polypeptide sequence that has at least 95% identity to the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 and differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by the substitution of an amino acid other than alanine at an amino acid residue position corresponding to position 65 of the polypeptide sequence of wild-type human B7-1 (SEQ ID NO:278), wherein said polypeptide variant has a CTLA-4/CD28 binding affinity ratio greater than the CTLA-4/CD28 binding affinity ratio of the extracellular domain of the wild-type primate B7-1.

Amended claim 335 recites more specifically an isolated or non-naturally occurring polypeptide variant of a mature domain of a wild-type primate B7-1 comprising a polypeptide sequence that has at least 95% identity to the polypeptide sequence of the mature domain of the wild-type primate B7-1 and differs from the polypeptide sequence of the mature domain of the wild-type primate B7-1 by the substitution of an amino acid other than alanine at an amino acid residue position corresponding to position 65 of the polypeptide sequence of wild-type human B7-1 (SEQ ID NO:278), wherein said polypeptide variant has a CTLA-4/CD28 binding affinity ratio greater than the CTLA-4/CD28 binding affinity ratio of the mature domain of the wild-type primate B7-1.

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Amended claim 342 specifies more particularly an isolated or non-naturally occurring polypeptide variant of a wild-type primate B7-1 comprising a polypeptide sequence that has at least 95% identity to the full-length polypeptide sequence of the wild-type primate B7-1 and differs from the polypeptide sequence of the wild-type primate B7-1 by the substitution of an amino acid other than alanine at an amino acid residue position corresponding to position 65 of the sequence of human B7-1 (SEQ ID NO:278), wherein said polypeptide variant has a CTLA-4/CD28 binding affinity ratio greater than the CTLA-4/CD28 binding affinity ratio of the wild-type primate B7-1.

These amended claims specify defined common structure that must be maintained by members of the genus and thus the rejection is overcome. Withdrawal of the rejection is respectfully requested.

Claims 327, 340, and 347 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *Id.* at p. 6. Specifically, the Examiner finds that "[t]he specification discloses B7-1 polypeptide variants which induce less T cell proliferation compared to wild-type B7-1 when used to costimulate T cells in soluble anti-CD3 induced proliferation assays" (citing page 220 bottom paragraph). *Id.* The Examiner is of the view that a "person of skill in the art is not enabled to make and use polypeptide variants which induce less T cell proliferation compared to wild-type B7-1 in the absence of primary T cell activation stimuli such as anti-CD3 antibodies, because it was well known at the time the invention was made that B7 molecules do not induce appreciable proliferation of T cells in the absence of [sic] primary T cell activation stimuli" (citing Linsley et al., 1996 and US Pat. No. 5,580,765). *Id.* at pp. 6-7. Based on these findings, the Examiner concludes that Applicants do not provide "a sufficiently enabling disclosure regarding how to make and use the generically recited B7-1 polypeptide variants which induce less T cell proliferation compared to wild-type B7-1." *Id.* at p. 7.

This rejection is traversed in part and overcome in part by the amendments to claims 321, 335, and 342. It was well known at the time the invention that wild-type B7-1 molecules are *costimulatory* molecules that are expressed on antigen-presenting cells. See., e.g., the specification, including at, but not limited to, e.g., page 1, line 29 to page 3, line 2. Each of CTLA-4 and CD28, which are expressed on T cells, is a ligand for the wild-type B7-1. *Id.* See also Fig. 1. It was also well known at the time the invention was made that T cell activation is initiated *in vivo* when a wild-

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type B7-1 binds one of these ligands expressed on the surface of the T cells and the T cells recognize their specific antigen (Ag) in the context of major histocompatibility complex (MHC) molecules expressed on the antigen-presenting cells. See, e.g., page 1, line 29 to page 3, line 2. One signal is provided by the interaction between B7-1 and CD28 or CTLA-4 ligand, and a second costimulatory signal is provided by the interaction between the T cell receptor and antigenic peptide presented in the groove of the MHC molecule. *Id.* See also Fig. 1. As explained throughout the specification, a T cell proliferation response can be measured *in vitro* for a polypeptide variant by using, e.g., an antigen (such as PHA) or anti-CD3 antibody to provide the second costimulation signal. See, e.g., page 42, lines 15-25; page 207, lines 15-23; page 234, lines 10-11; and page 237, lines 2-3. (PHA is defined on page 29, line 20.) Examples of such assays are provided in the specification. Those of ordinary skill in the art would understand that the T cell proliferation results of such assays provide correlation with the results determined *in vivo*. That such assays utilizing CD3 Abs and PHA antigen to assess T cell proliferation of B7 molecules were well known and commonly used is confirmed by US Pat. No. 5,580,765 (see, e.g., Cols. 32-34).

There is clearly sufficient disclosure in the specification through illustrative examples, terminology, and discussion to teach one of ordinary skill in the art how to make and use the claimed polypeptide variants without undue experimentation. The specification provides unambiguous guidance as to how to make and use the claimed polypeptide variants, including how to determine whether such polypeptides possess the specified activities, such as determining whether a polypeptide variant induces less T cell proliferation compared to T cell proliferation induced by the extracellular domain, mature domain, or full length sequence of wild-type primate B7-1, as in claims 327, 340 and 347, respectively. Furthermore, that some experimentation may be necessary does not preclude enablement. Given the relatively high level of skill of those in the pertinent art and the state of the art at the time, one of skill would plainly have been able to make and practice the claimed invention based upon Applicants' detailed disclosure without excessive experimentation. Based upon the detailed teachings of Applicants' specification, any experimentation would certainly not be undue. For at least these reasons, Applicants believe the rejection is improper and respectfully request that it be withdrawn.

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**V. REJECTION UNDER 35 USC § 102(B).**

Claims 321, 323, 335, 337, 342, 344, 348 and 335 [sic] were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Knauf et al., US Patent No. 5,475,099. Office Action, p. 7. In particular, the Examiner takes the view that the instant claims read on any polypeptide which does not have an alanine or tyrosine at position 65. *Id.* at p. 8. This rejection has been overcome by the amendments to claims 321, 335, and 342 discussed above. Withdrawal of the rejection is respectfully requested.

Claims 321-323, 327, 329-331, 333, 335-337, 342-344, 348, and 350 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Freeman et al., US Patent No. 6,084,067. Office Action, p. 8. The Examiner takes the position that Freeman et al. teach a costimulatory polypeptide, B7-2, which has a phenylalanine at the position that corresponds to position 65 of wild-type human B7.1. *Id.* This rejection has been overcome by the amendments to claims 321, 335, and 342 discussed above. Withdrawal of the rejection is respectfully requested.

**VI. REJECTION UNDER DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING.**

Claims 321-350 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 259-301, 368, 382-391 of copending application USSN 09/888,324 and claims 259, 269-273, 306-308, and 332-3338 [sic] of copending application USSN 10/479,901. Office Action, p. 9. The Examiner finds that "[w]hile the instant and copending claims do differ in certain structural (e.g., amino acid substitutions) and functional characteristics (e.g., CD28/CTLA4 binding affinity ratio), the instant and copending claims appear to be drawn to the same or nearly the same B7 molecules.

Applicants respectfully submit that the Examiner has not established a proper *prima facie* case of obviousness-type double patenting for each of rejected claims 321-350 in view of each of the cited copending applications. An obviousness-type double patenting rejection is analogous to a rejection for obviousness under 35 U.S.C. § 103, except that the application principally underlying the rejection is not considered prior art. In an obviousness-type double patenting rejection, the issue is whether the claim(s) of a pending application are obvious over the claim(s) of an issued patent or copending application. To establish a proper *prima facie* case of obviousness-type double patenting for each of the rejected claims, the requirements for obviousness must be met. See, e.g., MPEP §

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2143. Applicants respectfully submit that a *prima face* case of obviousness has not been sufficiently established for each of claims 321-350.

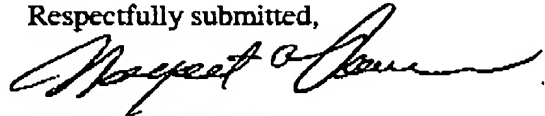
Furthermore, although Applicants do not concede a case of obviousness can be made for each of pending claims 321-350 over the recited claims of copending USSN 09/888,324 or at least claims 259, 306-308 and 332-338 of copending USSN 10/479,901, to the extent such double-patenting rejection can be made and is proper, the rejection has been overcome by the amendments to claims 321, 335, and 342.

Nevertheless, in an abundance of caution and in an effort to expedite prosecution of the application, Applicants will consider the filing of a terminal disclaimer with respect to the foregoing copending applications contingent upon the Examiner's entry of the amendment provided herein and withdrawal of all rejections and objections of record, should the terminal disclaimer be appropriate at that time.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application in any way, the Examiner is invited to telephone the undersigned at (650) 298-5809.

Respectfully submitted,



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